Surfactants today and tomorrow

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To date three types of surfactant for replacement therapy have been developed: animal derived (or natural) surfactant, synthetic surfactant (protein-free and no longer available) and reconstituted surfactants – consisting of a synthetic phospholipid matrix with the addition of artificial surfactant proteins or compounds mimicking them. Surfactant treatment has been shown to reduce mortality in premature infants with RDS. It also has been studied in other pulmonary disorders such as ARDS and MAS. Animal derived surfactants have been shown to produce better outcomes, fewer pulmonary airleaks and improved survival, compared with synthetic surfactants.

Between 2000 and 2005 a significant number of clinical trials of surfactant replacement therapy for neonates with RDS were reported in the medical literature[1]. Of the 87 papers reported, 31 were well-designed randomised controlled trials, 29 of which were in preterm infants with RDS and two in term infants with MAS. A total of 11 different surfactants were compared across 18 trials confirming that natural surfactant preparations were generally more efficacious than synthetic surfactants. Of note, not all natural surfactants are of similar efficacy and they may differ in terms of their clinical effects and costs.

Surfactant in preterm infants with RDS

In preterm infants, surfactant replacement therapy has been shown to significantly improve survival and reduce the incidence of RDS. Survival outcomes were similar for Curosurf (poractant alfa) and Surfaxin® (lucinactant) in a multicentre, randomised, controlled, non-inferiority trial which was stopped early because of poor recruitment rates and financial problems[2]. In this trial 243 infants of 24 to 28 weeks' gestational age who were successfully intubated at birth were randomised to treatment with either 175 mg/kg of Curosurf 2.2 mL/kg or Surfaxin 5.8 mL/kg within 30 minutes. Infants were stratified by birthweight (600 to 1000 g *vs* 1001 to 1250 g) and study centre. The primary endpoint, proportion of surviving infants without BPD, was similar for Surfaxin and Curosurf at 28 days (37.8 *vs* 33.1% respectively) and also at 36 weeks corrected age (64.7 *vs* 66.9% respectively). Larger studies would be needed to show significant differences between these two surfactant preparations.

Data from two randomised controlled comparative trials of Infasurf® (calfactant: 105 mg/kg) and Survanta® (beractant: 100 mg/kg) indicate that these agents are probably similarly effective in the prophylaxis and treatment of preterm infants[3]. Preterm infants enrolled in both trials had a maximum of three treatments at least 6 hours apart if they required >30% oxygen and were still intubated. The primary endpoint for both studies was the proportion of infants surviving at 36 weeks corrected age without needing oxygen. Approximately 750 infants, stratified according to gestational age (23 to 26 *vs* 27 to 29 wk) and birthweight, were enrolled in the prophylaxis trial; the primary endpoint was reached in 52% of infants in each treatment arm. In the other trial, over 1300 infants <36 hours old who required IPPV with >40% oxygen were stratified according to birthweight (401 to 750 g *vs* 751 to 1250 g *vs* 1251 to 2000 g). An interim analysis confirmed that the proportion of infants surviving without oxygen at 36 weeks was 57% with Infasurf and 59% with Survanta[3]. The investigators concluded that inadequate sample sizes and early trial closures prevent acceptance or rejection of the null hypothesis. Until large-scale randomised clinical trials can be successfully completed, questions regarding the differences among effective natural surfactant preparations will remain unanswered.

Surfactant plus CPAP in preterm infants with RDS

In the management of preterm infants with RDS, NCPAP is increasingly being viewed as an alternative to intubation and ventilation. It is a more gentle ventilatory technique and should reduce the incidence of ventilatory-mediated trauma and the need for intubation, both well known precursors of BPD.

Surfactant plus NCPAP improves lung function in very preterm infants with RDS[4]. Twenty-seven preterm infants of gestational age <30 weeks (inborn and aged <6 hours) with RDS on CPAP (4 to 7 cm water) and >30% oxygen were, following 200 mg/kg of Curosurf, randomised to either CPAP or IPPV (extubated when oxygen <40% and mean airway pressure <6 cm water). The primary endpoint, need for IPPV at 7 days, was not reached by any infant in the CPAP group but 43% of those on IPPV remained on ventilation at 1 week (p<0.03). Surfactant followed by CPAP was also associated with a reduction in the durations of oxygen, CPAP, IPPV and hospital stay, and a lower requirement for surfactant and reduced treatment costs[4].

Surfactant improves survival in very preterm infants

Evidence from the NICHD Neonatal Research Network collected in the 1990s indicates that use of surfactant treatment in very preterm infants (<25 weeks' gestational age) has significantly increased and this, along with greater use of prenatal steroids and prenatal antibiotics, is associated with improved survival *(Table 1)*[5]. However, the increase in survival has been associated with a greater risk of BPD and this may be an explanation for the increasing use of postnatal steroids up to 1998 in this Neonatal Research Network.

Table 1. NICHD Network outcomes data.

	1991 to 1994 (n=1408)	1995 to 1998 (n=1348)	P-value
Survival (%)	36.9	43.3	0.001
Prenatal steroids (%)	13.4	54.6	0.0001
Prenatal antibiotics (%)	39.2	67.8	0.0001
Caesarean section (%)	19.5	26.3	0.0001
Surfactant (%)	58.2	68.6	0.0001
BPD (%)	50.1	60.0	0.0001
Postnatal steroids (%)	41.1	57.7	0.0001

It is clear that the increased, and earlier, use of surfactant has improved survival at the expense of an increased risk of BPD but is this a persistent finding in the 2000s? Data from Belfast for extremely low gestational age neonates (ELGANS<28 weeks' gestation) show that this trend is continuing despite reduced use of postnatal steroids *(Table 2)*[6].

Table 2. ELGANS in Belfast study.

	1994 (n=87)	2004 (n=156)	P-value
Surfactant use (%)	44	90	0.0001
First dose at (min) Median (IQR)	180 (122-275)	9 (5-15)	0.0001
Survival (%)	67	80	0.04
Oxygen at 28 days (%)	49	66	0.05
Oxygen at 36 weeks (%)	14	31	0.05
Dexamethasone use (%)	21	1	0.0001
Hospital stay (days) Median (IQR)	47 (10-73)	44 (27-70)	NS

Surfactants differ in terms of cost-savings

A cost-minimisation study[7] based on two randomised controlled trials[8, 9] suggests that greater cost savings are associated with use of Curosurf than with use of Survanta. Modelling analyses determined that on the basis of single-dose vials and mean birthweight relative to Survanta, Curosurf was associated with cost savings of $618 to $950 per infant. When modelling analyses were based on individual birthweights, Curosurf was associated with smaller cost savings, in the order of $180 to $220 per infant[7].

Conclusions

Surfactant treatment is a proven effective and cost effective treatment for preterm infants with or at risk of developing RDS. It is best used early in the course of the disease and if combined with CPAP shortens the time on IPPV. Natural surfactants are superior to the first generation of synthetic surfactants but as yet, there is no clear evidence for superiority of the new synthetic surfactants over natural surfactant. It is clear, however, that surfactant, in addition to other interventions, improves the outcomes for preterm infants <28 weeks' gestation (and even <25 weeks) but with an increase in BPD. Further trials investigating the effect of early CPAP and surfactant are needed, as are more comparative trials evaluating the newer synthetic surfactants. Non-invasive administration of surfactant either by nebulisation or pharyngeal deposition or laryngeal mask may further improve outcomes by reducing the need for intubation. The next generation of clinical trials may investigate the effects of combination therapy with surfactant plus corticosteroids, antibiotics, antifungal agents, immunoglobulins and antioxidants and the results of these studies are awaited with interest.

References

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